Dental Research Journal

Original Article

Salivary oxidative stress in oral lichen planus treated with triamcinolone mouthrinse

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ABSTRACT

Background: Total antioxidant capacity (TAC) and malondialdehyde (MDA) levels have not been reported in oral lichen planus (OLP) patients treated with a topical corticosteroid. This study evaluates TAC and MDA levels in unstimulated saliva of OLP patients. Such measurements may need to be supported by clinical observation.

Materials and Methods: Twenty patients with OLP participated in a study conducted at the Department of Oral Medicine, Tehran University of Medical Sciences. Salivary TAC and MDA were determined by biochemical analyses before and after 5-week triamcinolone acetonide (0.2%) mouthrinse treatment. Subjective symptoms as well as lesion status pre- and post-treatment were measured using visual analog scale (VAS) and clinical scoring system, respectively. Wilcoxon signed rank test was used for the evaluation of MDA and TAC parameters, VASs, and rates of clinical scores. Spearman's rank correlation was used to determine the relationship between different variables.

Results: A statistically significant increase in salivary TAC was found after treatment. There was no significant difference in the reduction of salivary MDA levels in OLP patients after treatment.

Conclusion: Posttreatment analyses revealed a significant degree of recovery and pain relief of OLP lesions. Hence, triamcinolon mouthrinse by reducing oxidative stress is an appropriate treatment in OLP patients.

Key Words: Malondialdehyde, oral lichen planus, oxidative stress, triamcinolone acetonide

Received: January 2016
Accepted: January 2017

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INTRODUCTION

Oral lichen planus (OLP) is a chronic inflammatory mucosal disease of unknown etiology which can cause symptoms ranging from a burning sensation to severe pain interfering with speaking, eating, and swallowing.[1] The typical age of presentation is between 30 and 60 years, the disease is more frequently seen in women, and the most affected sites are the buccal mucosa, tongue, and the gingiva. There are no effective means to prevent OLP.[2] The possible malignant transformation of OLP is the subject of current discussions in literature.[3,4]

Free radicals, including reactive oxygen species (ROS) and reactive nitrogen species (RNS), exist in normal cells at low concentrations. An uncontrolled production of ROS/RNS results in

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How to cite this article: Mansourian A, Agha-Hosseini F, Kazemi HH, Mortazavi N, Moosavi MS, Beytollahi J, *et al*. Salivary oxidative stress in oral lichen planus treated with triamcinolone mouthrinse. Dent Res J 2017;14:104-10.

oxidative stress status.[5] Oxidative stress may be defined as a violation in balance between oxidants and reductants in living organisms. The efficiency of antioxidants is expressed as total antioxidant capacity (TAC) parameter, summarizing overall activity of all types of antioxidants in living systems.[6] Such a parameter may alternate the costly and time-consuming assays of individual antioxidant species as exogenous antioxidants (e.g., carotenoids, ascorbic acid, tocopherols, folic acid); endogenous antioxidants (e.g., catalase, superoxide dismutase, glutathione peroxidase, reduced glutathione, ferritin); and synthetic antioxidants (e.g., penicillinamine).[7]

Saliva may be considered the first line of defense against free radical-mediated oxidative stress, so the antioxidant capacity of saliva is of strategic interest.[8] As a diagnostic fluid which may be easily collected, saliva is used for the measurement of markers of oxidative stress associated with local oral conditions.[9,10] Lipoperoxidation has been considered a major presentation of oxidative stress. Malondialdehyde (MDA), as the lipid peroxidation marker, increases in an oxidative stress-dependent situation[11] and OLP.[12,13] Higher levels of MDA were reported in saliva of patients affected by OLP.[1,14]

To the best of our knowledge, pro-oxidant/antioxidant parameter change following a topical corticosteroid treatment has not been reported yet. The aim of the present study was to evaluate the changes in the status of oxidative stress and antioxidant defense system in OLP. In a prospective study, patients were treated with a triamcinolone acetonide mouthrinse. MDA and TAC in saliva of patients prior to and after treatment were measured.

MATERIALS AND METHODS

This clinical trial was performed at the Department of Oral Medicine. This study was registered at IRCT.ir (IRCT2014092919133N1) which is a primary registry in the WHO Registry Network setup.

Patient selection

Twenty-seven patients, with clinically and pathologically proven OLP according to the revised, modified World Health Organization 2003 diagnostic criteria,[2,3] were enrolled in this study. The inclusion criteria required the following:

Presence of bilateral, frequently symmetrical lesions, erythematous, or ulcerative lesions in the presence of reticular lesions elsewhere in the oral mucosa, presence of well-defined band-like zones of inflammatory infiltration confined to the superficial part of the connective tissue consisting mainly of mature lymphocytes, signs of liquefaction degeneration in the basal layer cells, and the absence of dysplasia.

The exclusion criteria were as follows:

Not using any systemic or topical therapeutic for the past 3 months or 1 month, respectively, patients with systemic disease and systemic drug therapy such as beta-blockers, diuretics, and calcium channel blockers, also intake of immunosuppressive agents, any supplementary vitamin in the previous 3 months, and a history of smoking or alcohol intake at least 1 month prior to the study were excluded from the study.[15,16] Patients with lichenoid lesions associated with drugs or restorations as well as the presence of any dermatological involvement of OLP were also excluded from the study.

A biopsy specimen was taken from each patient to confirm the diagnosis. Verified OLP patients (twenty patients) were then prepared for saliva collection.

Saliva collection and antioxidant assays

Participants in the study were evaluated under the same protocol. They attended the Department of Oral Medicine, between 10:00 and 12:00 a.m. Samples were collected at the same time of the day (10–12 a.m.) and at least 2 h after the last intake of food or drink.[17] Prior to saliva collection, patients were asked to rinse the mouth with distilled water. Five milliliters of unstimulated whole saliva was then collected through spitting method into a graded sampling tube. Immediately after collection, saliva samples were centrifuged at 2000 g for 10 min at +4°C. The supernatants were also drawn and stored at −80°C until further analysis. All patients were prescribed a suspension of triamcinolone acetonide 0.2%, four times a day, for 5 weeks. Patients were instructed to rinse with 5 ml of mouthrinse for 3 min and then to expectorate, and were also instructed not to eat or drink until 30 min after usage. All patients were placed on follow-up period during 2, 4, and 5 weeks after starting the treatment. Saliva collection procedure was repeated at the end of 5-week therapy.

The TAC of saliva was determined by measuring its ability to decolorize 2,2'-azinobis (3-ethylbenzothiazoline-6-sulfonic acid) radical

cation (ABTS+). In brief, in this method, the ABTS is oxidized to ABTS+ (deep green) using hydrogen peroxide in acidic medium (the acetate buffer 30 mmol/L pH 3.6). Antioxidants accelerate the bleaching rate of ABTS+ in the acetate buffer 0.4 mol/L pH 5.8 medium to a degree proportional to their concentrations. This change in color is measured as a change in absorbance at 660 nm. The results were expressed as μmol trolox equivalent/L according to a standard curve, which was prepared with a serial dilution of trolox.[18]

The saliva MDA level, which is the end product of the oxidation of polyunsaturated fatty acids, was measured based on reaction with thiobarbituric acid (TBA) at 90–100°C.[19] MDA and TBA react together, in the TBA test reaction, to make a pink pigment with an absorption maximum at 532 nm. The reaction was completed at pH 2–3 at 90°C for 15 min. Precipitate protein was made by mixing sample with two volumes of cold 10% (w/v) trichloroacetic acid. They centrifuged and reacted with an equal volume of 0.67% (w/v) TBA in a boiling water bath for 10 min. The absorbance was read at 532 nm. The results were stated as μmol/1 consistent with a standard curve.

This study was approved by the Review Board, and written informed consent was obtained from all patients prior to saliva collection and prior to treatment. During the study, three patients who developed candidiasis were treated by an antifungal drug (nystatin). These patients were excluded from the study because their treatments might have affected the results. Four patients with poor compliance were also excluded from the study. For ethical considerations, treatment was continued for active or excluded patients who still had complaints after the 5 weeks of therapy. All patients were given instruction regarding the disease and the planned treatment.

Assessment parameters

The changes in the subjective symptoms were evaluated with the use of visual analog scale (VAS) on a 0–100 scale. Prior to the treatment and at the end of the 5-week follow-up, VAS was recorded for all the patients.

Severity of the disease (objective response) was assessed by a semi-quantitative scoring system based on site and area,[20] with moderate modification by adding the right and left borders of the tongue, also considering gingiva as the upper and lower parts. Grading based on score was modified, and the maximum score was changed from 12 to 15.[20] Table 1 demonstrates the basic scoring/grading system used by Malhotra *et al*. but with moderate modification.

Statistical analysis

Wilcoxon signed rank test was used for the evaluation of MDA and TAC parameters prior and after treatment. This test, also, was used to analyze VASs and rates of clinical involvements (scores) prior to and after treatment. Spearman's rank correlation was used to determine the relationship between different variables.

RESULTS

Twenty confirmed OLP patients (16 women, four men), with a mean age of 48.20 years, were evaluated in the present study. The mean duration of the

Table 1: Modified Malhotra *et al*.'s clinical scoring system

Scoring site	Area involved	Points
Buccal mucosa		
Right side	<50%	1
	≥50%	2
Left side	<50%	1
	≥50%	2
Tongue		
Back surface	<50%	1
	≥50%	2
Front surface	<50%	1
	≥50%	2
Right border	Involved	1
	Uninvolved	0
Left border	Involved	1
	Uninvolved	0
Lips		
Upper	Involved	1
	Uninvolved	0
Lower	Involved	1
	Uninvolved	0
Gingiva		
Upper	Involved	1
	Uninvolved	0
Lower	Involved	1
	Uninvolved	0
Palate	Involved	1
	Uninvolved	0
Maximum score	15	
Grading (based on score)		
Grade 0	0	
Grade I	1-4	
Grade II	5-9	
Grade III	10-15	

disease was 11.50 months before entering the study. Distribution frequency of the lesions under the study is shown in Table 2.

Mean VAS score prior to treatment was 3.90 ± 2.17, and after treatment, it was 0.90 ± 1.48. The difference was statistically significant ($P < 0.001$). In this study, bivariate correlations between TAC, MDA, VAS, and duration of disease were not statistically significant ($P > 0.05$).

The mean level of unstimulated whole saliva MDA in OLP patients prior to the treatment was higher than that of the treated patients as shown in Table 3 and Figure 1. However, the difference was not statistically significant ($P = 0.380$). The mean level of salivary TAC in OLP patients who received the treatment was promoted. This difference was statistically significant ($P = 0.028$). Table 3 and Figure 2 represent such a significant increase in TAC level prior to and after the treatment.

Based on the modified scoring system (0–15), clinical scores were 2–10 (mean = 4.80 ± 1.93) before and 0–6 (mean = 2.15 ± 1.66) after the treatment. The difference was statistically significant ($P < 0.001$), which was an indication of clinical improvement. Out of the twenty patients who participated in our study, improvement of clinical score was noted in 14 patients (70%) at the end of 5-week treatment by mouthrinse. Grade 0 or complete healing of Grade I was observed in four patients (20%), indicating that the whole lesion resolved and normal mucosa was regained. Change of Grade II to Grade I in nine patients (45%) and Grade III to Grade II in one patient (5%) were observed.

Absolute/relative distribution frequencies of clinical grades prior to and after treatment are shown in Table 4.

DISCUSSION

According to the literature, OLP involves primarily middle-aged adults, and the lesions are more frequent in women.[2,10,21] The present study revealed similar gender difference, i.e., 16 women compare to four men. Patients were in the age range between 32 and 68 years (mean = 48.20). Buccal mucosa involvement in the present study was predominantly bilateral, which is similar to other studies.[2,22]

According to van der Waal,[2] the reticular, erythematous (erosive), plaque type, and ulcerative type are the most common types; among them, the erythematous and ulcerative types are particularly painful. A VAS recording prior to and after treatment revealed a decline in the score of the most of our patients. Differences of both VAS scores and clinical scores were statistically significant ($P < 0.001$) and could account for a palliative effect at the end of 5-week treatment. The clinical and symptomatic improvements observed in the present study were comparable to those of Malhotra *et al's*., study who compared triamcinolone acetonide (0.1%) paste with an oral steroid (Betamethasone).[20] Their subjective responses appeared from 12th week; however, mean scores of objective responses appeared to be significant from 8th week afterward. From this viewpoint, the

Table 2: Distribution of absolute frequency and relative frequency of lesion forms, *n* (%)

Lesion Forms	*n* (%)
Erythematous	14 (70)
Ulcerative	6 (30)

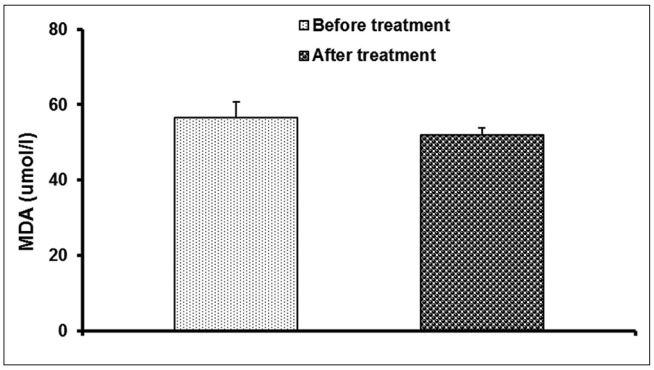

Figure 1: Concentration of malondialdehyde in unstimulated saliva of oral lichen planus patients before and after treatment with triamcinolone mouthrinse.

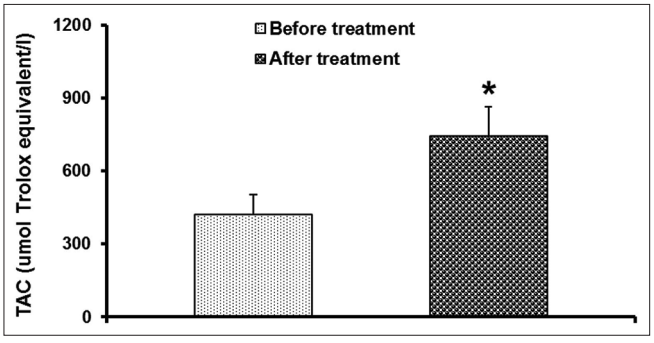

Figure 2: Concentration of total antioxidant capacity in unstimulated saliva of oral lichen planus patients before and after treatment with triamcinolone mouthrinse.

Table 3: Mean total antioxidant capacity (μmol/trolox) and malondialdehyde (μmol/L) prior to and after treatment (mean±standard deviation)

TAC/MDA Before and After Treatment	Number	Minimum	Maximum	Mean±SD
TAC before treatment	20	0.00	1302.26	421.54±368.18
TAC after treatment	20	181.82	2374.92	744.78±587.40
MDA before treatment	20	39.74	97.33	56.59±14.96
MDA after treatment	20	41.18	98.10	51.95±13.12

TAC: Total antioxidant capacity; MDA: Malondialdehyde; SD: Standard deviation

Table 4: Distribution of absolute frequency and relative frequency of lesion grades prior to and after treatment, *n* (%)

Grading	Prior to treatment (%)	After treatment (%)
0	0	4 (20)
1	9 (45)	14 (70)
2	10 (50)	2 (10)
3	1 (5)	0

results of their study can be compared to ours, in which the objective mean scores are significant following a 5-week corticosteroid mouthrinse treatment. According to our findings, four completely recovered cases, as well as changing Grade III and Grade II cases to Grade II and Grade I, respectively, indicate certain degrees of recovery following treatment. Topical corticosteroids are safe when applied to mucous membrane for short periods, but prolonged use can produce side effects such as adrenal suppression, secondary candidiasis, and rarely, atrophy of oral mucosa. Corticosteroids are the most effective agents in the treatment of OLP, and topical corticosteroids have been preferred over systemic corticosteroids, except during acute exacerbations.[20] However, there has been debate considering the application of such immunomodulating agents in OLP and oral lichenoid lesions.[3]

Free radicals and ROS are essential for biological processes. Tissue damage can occur when antioxidants do not efficiently counteract their action. The mouth is a critical site for oxidative stress due to frequent exposure to chemical, thermal, and microbial stimulants. With the advent of new technology, a blood drop, sample of urine or saliva can provide a generic value of the patient's oxidative stress, measuring the amount of free radicals.[11] Saliva is increasingly used and well validated in diagnosing, monitoring systemic health and disease states, predicting disease progression as well as detecting biomarkers.[15] Since the process of mastication promotes a variety of immunological reactions such as lipid peroxidation, saliva may be considered as the first line of defense against free radical-mediated oxidative stress.[8]

The literature shows how MDA is one of the most studied products of polyunsaturated fatty acid peroxidation, which increases in oxidative stress-dependent conditions.[11] Previous studies shown that MDA is increased in saliva of patients affected by OLP.[1,14] A systematic review published in 2014 concluded that there is a need for further studies with concentration on the prognostic value of MDA by evaluating its levels both pre- and post-treatment in OLP.[23] Our study with a declined MDA level following a topical corticosteroid therapy (although not statistically significant) resembles a recent study in Belgium, in which the effect of curcumin intake was assessed in OLP patients. Authors claimed that the lipid peroxidation decrease in patients with precancerous lesions due to the anti-precancerous effects of curcumin was mediated by pro- and anti-oxidative pathways.[24] A significant rise in salivary TAC level, which was found in our treated patients, was similar to a remarkable activity of total antioxidants in healthy controls of an OLP study by Ergun *et al*.[15] A significant increase in salivary TAC may also account for a reinforced antioxidant defense system at the end of a 5-week clinical trial. Such a significant rise in TAC may improve the balance in the pro-oxidant/antioxidant equilibrium. Formerly, it has been hypothesized that, in lichen planus lesions, antioxidant defense mechanisms are overwhelmed resulting in an increase of oxidative damage to lipids, proteins, and DNA, which may be involved in the inflammatory processes of the disease.[25]

Several studies have recently reported nuclear factor-kappa B (NF-κB) expression in OLP. As an inflammatory regulator, NF-κB may be activated by a variety of inflammatory signals, and some pro-inflammatory cytokines such as interleukin-1 β and tumor necrosis factor-α. NF-κB is one of the most important transcription factors whose activity can be influenced by oxidative stress.[26,27] NF-κB is

also inhibited by glucocorticoids and can be a target for novel anti-inflammatory therapies.[28] Recent studies suggest that defense mechanism reduction in lichen planus and the impaired oxidant/antioxidant balance may contribute to the pathophysiology of the disease.[1,15] Oxidative damage represents the main threat for the genome integrity in living organisms. ROS generation may also be prone to mutagenesis.[11] The importance of reactive oxygen and antioxidant species to human biology came from the realization that transcription factors, such as NF-κB and activating protein-1, were redox sensitive.[7] The activity of a redox-sensitive transcription factor is affected by oxidation. Kinases and tyrosine phosphatases, proposed as redox regulators of signaling machinery, regulate T-cell receptor signaling and successive phosphorylation cascade. Eventually, signaling complexes are formed which activate several signaling pathways such as the NF-κB pathway.[27,29]

CONCLUSION

Antioxidant drugs may reverse the increased oxidative stress status in lichen planus and result in clinical improvement. Based on oxidative stress modulation, the antioxidant defense must be part of a therapeutic strategy for OLP. Therefore, we propose drugs such as triamcinolone acetonide mouthrinse for such an increased oxidative stress status.

Financial support and sponsorship
Nil.

Conflicts of interest
The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or nonfinancial, in this article.

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